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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,223	01/09/2004	Franklin R. Cockerill III	20014-004002/22515	8045

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/21/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/754,223	COCKERILL ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *29-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-28 and 40-48* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :3/22/04;5/17/04;6/7/04;6/17/04;7/1/04;9/28/04;6/27/05.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-28 and 40-48) in the reply filed on October 9, 2008 is acknowledged.

2. Claims 29-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 9, 2008.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 1-28 and 40-48 will be examined.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on March 22, 2004; May 17, 2004; June 7, 2004; June 17, 2004; July 1, 2004; September 28, 2004 and June 27, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Specification

6. The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The hyperlinks are present on page 20, line 4; page 22, line 8 and page 26, line 9.

Appropriate correction is required.

Sequence Rules Compliance

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Applicants submitted a new sequence listing on June 25, 2008. However, no paper copy was submitted or a letter stating that the CRF and paper copies are the same. If the "paper" copy was submitted on CD-ROM, then the rules given in MPEP 2422.03 regarding the submission need to be followed:

"If the "Sequence Listing" is submitted on compact disc, the specification must contain an incorporation by reference of the material on the compact disc in a separate paragraph, identifying

each compact disc by the names of the files contained on each of the compact discs, their date of creation and their sizes in bytes (**37 CFR 1.52(e)**). The total number of compact discs including duplicates and the files on each compact disc shall be specified (**37 CFR 1.77(b)(4)**). The compact disc used to submit the sequence listing may also contain table information if the table has more than 50 pages of text. See **37 CFR 1.823(a)(2)** and **1.52(e)(1)(iii)**. The compact disc and duplicate copy must be labeled "Copy 1" and "Copy 2," respectively, and a statement stating that the copies are identical must be included. If the two compact discs are not identical, the Office will use the disc labeled "Copy 1" for further processing (**37 CFR 1.52(e)(4)). See also MPEP § 608.0**5.

The compact disc submitted under **37 CFR 1.821(c)** may, if it contains no tables, be identical to the computer readable form (CRF) submitted under **37 CFR 1.821(e)** and **37 CFR 1.824**, if that CRF is submitted on a compact disc. Even if the compact discs submitted under both **37 CFR 1.821(c)** and (e) are identical, each compact disc submitted under 37 CFR 1.821(c) must be submitted in duplicate, in addition to the CRF under **37 CFR 1.821(e)**."

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 8 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 8 is indefinite over the recitation of "… measuring the wavelength emitted by said acceptor fluorescent moiety". What is measured in FRET is the intensity of the light emitted by the acceptor at a certain wavelength, not the wavelength itself.

B) Claim 20 recites the limitation "said control sample comprises said portion of said portion of said IS481 nucleic acid molecule" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Neither claim 1 nor claim 19, from which claim 20 depends, contain a limitation "portion of IS481 nucleic acid molecule".

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993).

Regarding claim 46, Van der Zee et al. teach a method for detecting the presence or absence of B. pertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a dye-binding step, wherein said amplifying step comprises contacting said sample with a pair of IS481 primers to produce an IS481 amplification product if a B. pertussis IS481 nucleic acid molecule is present in said sample, wherein said dye-binding step comprises contacting said IS481 amplification product with a nucleic acid binding dye (Van der Zee et al. teach amplification of B. pertussis in samples from patients to detect the presence or absence of B. pertussis (Abstract). The samples were amplified with a pair of IS481-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). The amplification products were contacted with

ethidium bromide (= dye) by electrophoresing them on a gel containing the dye (page 2136, fifth paragraph).); and

detecting the presence or absence of binding of said nucleic acid binding dye to said amplification product (Van der Zee et al. teach detection of the amplification products (Fig. 3 and 4).),

wherein the presence of binding is indicative of the presence of B. pertussis in said sample, and wherein the absence of binding is indicative of the absence of B. pertussis in said sample (Van der Zee et al. teach that the presence of a 288 bp amplification product indicates presence of B. pertussis in the sample; Fig. 3, 4; Table 3; page 2138, last paragraph; page 2139, first paragraph).).

Regarding claim 47, Van der Zee et al. teach ethidium bromide (page 2136, fifth paragraph).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 4-14, 18-20, 22, 25-28 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670).

A) Claims 1 and 40 will be considered together in the rejection. Claim 1 is drawn to detection of B. pertussis using a pair of IS481 primers and two IS481 probes, claim 40 is drawn to detection of B. pertussis using a pair of IS481 primers and one IS481 probe.

Regarding claims 1 and 40, Van der Zee et al. teach a method for detecting the presence or absence of Bordetella pertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises contacting said sample with a pair of IS481 primers to produce an IS481 amplification product if a B.pertussis IS481 nucleic acid molecule is present in said sample, wherein said hybridizing step comprises contacting said sample with a pair of IS481 probes, wherein the members of said pair of IS481 probes hybridize within no more than five nucleotides of each other, wherein a first IS481 probe of said pair of IS481 probes is labeled with a donor fluorescent moiety and a second IS481 probe of said pair of IS481 probes is labeled with a corresponding acceptor fluorescent moiety (Van der Zee et al. teach amplification of B. pertussis in samples from patients to detect the presence or absence of B. pertussis (Abstract). The samples were amplified with a pair of IS481-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). Amplification products are detected with a digoxigenin-labeled probe specific for IS481 sequences (page 2136, fourth and fifth paragraphs).); and

detecting the presence or absence of fluorescence resonance energy transfer (FRET) between said donor fluorescent moiety of said first IS481 probe and said corresponding acceptor

fluorescent moiety of said second IS481 probe (Van der Zee et al. teach detection of the amplification products with the labeled probe (Fig. 5).).

Regarding claim 18, Van der Zee et al. teach biological sample in a form of nasopharyngeal swab (page 2135, last paragraph).

Regarding claim 19, Van der Zee et al. teach using a control sample in the amplification reaction (page 2136, third paragraph; Fig. 4; page 2138, second and third paragraphs).

Regarding claim 20, Van der Zee et al. teach the control sample having a portion of the IS481 sequence, since it contains a fragment of E. coli DNA amplified with BP1 (IS481-specific) primer (page 2136, third paragraph; page 2138, second and third paragraphs).

Regarding claim 22, Van der Zee et al. teach a method for detecting the presence or absence of Bordetella parapertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises contacting said sample with a pair of IS1001 primers to produce an IS1001 amplification product if a B. parapertussis IS1001 nucleic acid molecule is present in said sample, wherein said hybridizing step comprises contacting said sample with a pair of IS1001 probes, wherein the members of said pair of IS1001 probes hybridize within no more than five nucleotides of each other, wherein a first IS1001 probe of said pair of IS1001 probes is labeled with a donor fluorescent moiety and a second IS1001 probe of said pair of IS1001 probes is labeled with a corresponding acceptor fluorescent moiety (Van der Zee et al. teach amplification of B. parapertussis in samples from patients to detect the presence or absence of B. parapertussis (Abstract). The samples were amplified with a pair of IS1001-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). Amplification products are

detected with a digoxigenin-labeled probe specific for IS1001 sequences (page 2136, fourth and fifth paragraphs).); and

detecting the presence or absence of fluorescence resonance energy transfer (FRET) between said donor fluorescent moiety of said first IS1001 probe and said corresponding acceptor fluorescent moiety of said second IS1001 probe (Van der Zee et al. teach detection of the amplification products with ethidium bromide (Fig. 3, 4) and teach detection of amplification products with the probes (Fig. 5).).

Regarding claim 25, Van der Zee et al. teach a method for detecting the presence or absence of Bordetella pertussis and/or Bordetella parapertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises contacting said sample with a pair of IS481 primers and a pair of IS1001 primers to produce an IS481 amplification product if a B. pertussis IS481 nucleic acid molecule is present in said sample and an IS1001 amplification product if a B. parapertussis IS1001 nucleic acid molecule is present in said sample, wherein said hybridizing step comprises contacting said sample with a pair of IS481 probes and a pair of IS1001 probes, wherein the members of said pair of IS481 probes hybridize within no more than five nucleotides of each other and wherein the members of said pair of IS1001 probes hybridize within no more than five nucleotides of each other, wherein a first IS481 probe of said pair of IS481 probes is labeled with a donor fluorescent moiety and a second IS481 probe of said pair of IS481 probes is labeled with a corresponding acceptor fluorescent moiety, wherein a first IS1001 probe of said pair of IS1001 probes is labeled with a donor fluorescent moiety and a second IS1001 probe of said pair of IS1001 probes is labeled with a corresponding acceptor fluorescent moiety (Van der Zee et al.

teach simultaneous amplification of B. pertussis and B. parapertussis in samples from patients to detect the presence or absence of B. pertussis and/or B. parapertussis (Abstract). The samples were amplified with a pair of IS481-specific primers and pair of IS1001-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). Amplification products are detected with a digoxigenin-labeled probe specific for IS481 or IS1001 sequences (page 2136, fourth and fifth paragraphs; Fig. 5).); and

detecting the presence or absence of fluorescence resonance energy transfer (FRET) between said donor fluorescent moiety of said first IS1001 probe and said corresponding acceptor fluorescent moiety of said second IS1001 probe (Van der Zee et al. teach detection of the amplification products with ethidium bromide (Fig. 3, 4) and teach detection of amplification products with the probes (Fig. 5).).

B) Van der Zee et al. do not teach detection of amplification products with a probe consisting of two segments, one of which is labeled with donor and the other with acceptor, or limitations of claims 4-14, 26-28, 41 or 42.

C) Wittwer et al. teach real-time detection of amplification products.

Regarding claims 1, 22 and 25, Wittwer et al. teach detection of amplification products in real time by using two probes, one labeled with a fluorescent donor, the other with a fluorescent acceptor (col. 5, lines 21-41; Fig. 5C). The probe detection utilizes the fluorescence resonance energy transfer (FRET) (col. 19, lines 40-63). The fluorescence is monitored for both of the fluorophores (col. 21, lines 58-65). The probes were used to monitor amplification of different starting amounts of beta-globin. The presence of FRET between the two fluorophores was indicative of the presence of nucleic acid template in the sample (col. 30, lines 30-60, col. 31, lines 22-28; Fig. 17). The optimum spacing of the probes is from zero to 5 bases (col. 28, lines 8-26).

Regarding claims 4, 5 and 42, Wittwer et al. teach that the optimum spacing of the probes is from zero to 5 bases, with the highest signal occurring with one base between the probes (col. 28, lines 8-26; Fig. 12).

Regarding claim 6, Wittwer et al. teach the donor moiety being fluorescein (col. 25, lines 62-65; col. 28, lines 8-26).

Regarding claim 7, Wittwer et al. teach the acceptor moiety being Cy5 or Cy5.5 (col. 26, lines 5-26, 28-67; col. 27, lines 1-10, 20-27; col. 28, lines 8-26).

Regarding claim 8, Wittwer et al. teach detection by exciting the sample at a wavelength absorbed by the donor and measuring the intensity of the fluorescence emitted by the acceptor (col. 21, lines 60-65; Fig. 8; col. 27, lines 5-10; Fig. 9).

Regarding claim 9, Wittwer et al. teach quantitation of FRET (col. 21, lines 60-65; Fig. 8; col. 27, lines 5-10; Fig. 9; Fig. 17).

Regarding claims 10 and 11, Wittwer et al. teach detection of the fluorescent signal in real time and after each cycling step (col. 30, lines 30-60; col. 31, lines 22-28; Fig. 17).

Regarding claims 12-14, Wittwer et al. teach that the number of steps after which FRET signal is detectable depends on the template concentration (Fig. 17, for example). Therefore, 10^4 copies of the template can be detected after 25 cycles, whereas 10^3 copies are detected after 30 cycles, and 10 and 100 copies are detected after 40 cycles.

Regarding claims 26 and 27, Wittwer et al. teach discrimination of different templates by determining the melting temperature of the probes, to discriminate between homozygous and heterozygous individuals with wild-type and mutant DNA (either a single probe or a pair of probes) (col. 43, lines 40-67; col. 44; col. 45, lines 1-47; Fig. 46; col. 46, lines 19-48; Fig. 48).

Regarding claim 28, Wittwer et al. teach different acceptor moieties, e.g. rhodamine, Cy5 or Cy 5.5 (col. 25, lines 62-67; col. 26, lines 8-13; col. 27, lines 20, 21).

Regarding claim 41, Wittwer et al. teach amplification employing a polymerase having a 3'to 5' exonuclease activity (Fig. 5B; col. 30, lines 30-60; col. 31, lines 5-20; Fig. 15).

Regarding claim 43, Wittwer et al. teach the acceptor moiety, rhodamine, being a quencher (col. 30, lines 33, 34).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used FRET-based amplification detection techniques of Wittwer et al. in the B. pertussis and B. parapertussis detection method of Van der Zee et al. The motivation to do so, provided by Wittwer et al., would have been that PCR was performed rapidly and the reaction monitored continuously, allowing adjustment of parameters (col. 4, lines 15-18), the total time required for PCR amplification and analysis was decreased (col. 4, lines 27-31) and desired from undesired products and different amplification products were distinguished on the basis of melting curves (col. 5, lines 1-15).

15. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670).

A) Van der Zee teach detection of amplification products using ethidium bromide, but do not teach determination of the melting temperature between the amplification product and the nucleic acid binding dye.

B) Regarding claim 48, Wittwer et al. teach determination of the melting curves of three different amplification products using SYBRGreenI. The three fragments were amplified from hepatitis B surface antigen, PSA and beta-globin genes. They could be distinguished on the basis of the differences in their melting temperatures (col. 37, lines 49-67; col. 38, lines 1-27; Fig. 37).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used temperature melting profiles of Wittwer et al. in the method of Van der Zee et al. The motivation to do so was expressly provided by Wittwer et al. (col. 4, lines 64-67; col. 5, lines 1-11):

"In accordance with another aspect of the present invention, fluorescence monitoring is used to acquire product melting curves during PCR by fluorescence monitoring with double-strand-specific DNA specific dyes. Plotting fluorescence as a function of temperature as the thermal cycler heats through the dissociation temperature of the product gives a PCR product melting curve. The shape and position of this DNA melting curve is a function of GC/AT ratio, length, and sequence, and can be used to differentiate amplification products separated by less than 2° C in melting temperature. Desired products can be distinguished from undesired products, including primer dimers. Analysis of melting curves can be used to extend the dynamic range of quantitative PCR and to differentiate different products in multiplex amplification."

16. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670), as applied to claim 1 above, and further in view of Mc Lafferty et al. (J. Gen. Microbiol., vol. 134, pp. 2297-2306, 1988) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claim 2, Van der Zee et al. teach IS481-specific primers BP1 and BP4, hybridizing to bp 208-228 and 476-496 of IS481. Van der Zee et al. teach the primers based on an IS481 sequence of McLafferty et al. (page 2136, second paragraph). The sequence of McLafferty et al. is presented in the GenBank Accession No. M22031.

B) Van der Zee et al. do not specifically teach primers with SEQ ID NO: 1 and 2.

C) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 684-701 of the IS481 sequence of McLafferty et al., SEQ ID NO: 2 is complementary to bp 895-917 of the IS481 sequence of McLafferty et al.

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BPETERRA
LOCUS       BPETERRA                1053 bp    DNA     linear   BCT 26-APR-1993
DEFINITION  B.pertussis insertion sequence with 28 bp terminal inverted repeats
            DNA.
ACCESSION   M22031
VERSION     M22031.1  GI:144060
KEYWORDS    insertion sequence.
SOURCE      Bordetella pertussis
  ORGANISM  Bordetella pertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1  (bases 1 to 1053)
  AUTHORS   McLafferty,M.A., Harcus,D.R. and Hewlett,E.L.
  TITLE     Nucleotide sequence and characterization of a repetitive DNA
            element from the genome of Bordetella pertussis with
            characteristics of an insertion sequence
  JOURNAL   J. Gen. Microbiol. 134 (Pt 8), 2297-2306 (1988)
   PUBMED   2908119
COMMENT     Original source text: B.pertussis DNA.
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ORIGIN

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  Best Local Similarity   100.0%;  Pred. No. 91;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CCAGTTCCTCAAGGACGC 18
              ||||||||||||||||||
Db        684 CCAGTTCCTCAAGGACGC 701

BPETERRA/c
LOCUS       BPETERRA                1053 bp    DNA     linear   BCT 26-APR-1993
DEFINITION  B.pertussis insertion sequence with 28 bp terminal inverted repeats
            DNA.
ACCESSION   M22031
VERSION     M22031.1  GI:144060
KEYWORDS    insertion sequence.
SOURCE      Bordetella pertussis
  ORGANISM  Bordetella pertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
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            Alcaligenaceae; Bordetella.
REFERENCE   1  (bases 1 to 1053)
  AUTHORS   McLafferty,M.A., Harcus,D.R. and Hewlett,E.L.
  TITLE     Nucleotide sequence and characterization of a repetitive DNA
            element from the genome of Bordetella pertussis with
            characteristics of an insertion sequence
  JOURNAL   J. Gen. Microbiol. 134 (Pt 8), 2297-2306 (1988)
   PUBMED   2908119
COMMENT     Original source text: B.pertussis DNA.
FEATURES             Location/Qualifiers
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     repeat_region   1. .28
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     repeat_region   1026. .1053
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ORIGIN

  Query Match             100.0%;  Score 23;  DB 14;  Length 1053;
  Best Local Similarity   100.0%;  Pred. No. 0.41;
  Matches   23;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GAGTTCTGGTAGGTGTGAGCGTA 23
              |||||||||||||||||||||||
Db        917 GAGTTCTGGTAGGTGTGAGCGTA 895
```

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Van der Zee et al. and Wittwer et al. with the use of functionally equivalent primers selected from the sequence of McLafferty et al., since Van der Zee et al. expressly teach primer selection from the B. pertussis published sequence and since McLafferty et al. provide such published sequence.

In the decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because

homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. pertussis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

17. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670), as applied to claim 1 above, and further in view of Longo et al. (Gene, vol. 93, pp. 125-128, 1990).

A) Neither Van der Zee et al. nor Wittwer et al. teach preventing amplification of contaminating nucleic acid by performing amplification in the presence of uracil and uracil-DNA glycosylase.

B) Regarding claims 15-17, Longo et al. teach PCR amplification reaction with uracil and uracil-DNA glycosylase (UDG) (page 126, second and third paragraph; page 127, paragraphs 2-4; Fig. 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the method of preventing contaminant amplification of Longo et al. in the combined detection method of Van der Zee et al. and Wittwer et al. The motivation to do so, provided by Longo et al., would have been that using UTP and UDG prevented occurrence of false positive results in PCR (Abstract).

18. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670), as applied to claim 1 above, and further in view of McMillan (U.S. Patent No. 6,312,929).

A) Regarding claim 21, Van der Zee et al. teach an internal control, but do not teach control probes and primers different from the IS481 probes or primers.

B) McMillan teaches internal controls for amplification reactions (Abstract), which can be used in reactions with FRET, molecular beacon and TaqMan probes (col. 13, lines 1-6, 32-48; col. 14, lines 34-54). The amplification reaction contains two internal control probes (HP2 and HP3)

and a pair of control primers (P3 and P4), designed for two internal controls, IC1 and IC2, different from the target sequence (Fig. 1; col. 2, lines 66 and 67; col. 3, lines 1-38; col. 6, lines 16-63).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used a pair of control primers and a pair of control probes of McMillan in the detection method of Van der Zee et al. and Wittwer et al. The motivation to do so, provided by McMillan, would have been that using the internal controls allowed quantitation of the amplification reaction products in a single reaction and in real time (col. 16, lines 15-23).

19. Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (=Van der Zee1) (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993) and Wittwer et al. (U.S. Patent No. 6,174,670), as applied to claim 22 above, and further in view of Van der Zee et al. (=Van der Zee2) (J. Bacteriol., vol. 175, pp. 141-147, 1993) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999).

A) Regarding claims 23 and 24, Van der Zee1 teach IS1001-specific primers BPPA and BPPZ, hybridizing to bp 1211-1232 and 734-755 of IS1001, and a probe cut out from the IS1001 with PstI (page 2136, second and fourth paragraphs). Van der Zee1 teach that the primers based on a IS1001 sequence of Van der Zee2 (page 2136, second paragraph). The GenBank accession number for that sequence is X66858.

B) Van der Zee1 do not specifically teach primers with SEQ ID NO: 5 and 6 and probes with SEQ ID NO: 12 and 13.

C) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 375-392 of the IS1001 sequence of Van der Zee2, SEQ ID NO: 6 is complementary to bp 556-574 of the IS1001 sequence of Van der Zee2, SEQ ID NO: 12 is complementary to bp 470-488 of the IS1001

sequence of Van der Zee2, and SEQ ID NO: 13 is complementary to bp 490-504 of the IS1001 sequence of Van der Zee2 et al.

```
X66858
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
            transposase.
ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
            transposase.
SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
REFERENCE   2  (bases 1 to 1306)
  AUTHORS   van der Zee,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
            &, Environmental Protection, A Van Leeuwenhoeklaan 9, P O Box 1,
            3720 BA Bilthoven, THE NETHERLANDS
COMMENT     On Jul 10, 2002 this sequence version replaced gi:262329.
FEATURES             Location/Qualifiers
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Qy          1 GGCGATATCAACGGGTGA 18
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X66858/c
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
            transposase.
ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
            transposase.
SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
REFERENCE   2  (bases 1 to 1306)
  AUTHORS   van der Zee,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
            &, Environmental Protection, A Van Leeuwenhoeklaan 9, P O Box 1,
            3720 BA Bilthoven, THE NETHERLANDS
COMMENT     On Jul 10, 2002 this sequence version replaced gi:262329.
FEATURES             Location/Qualifiers
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Qy          1 CAGGGCAAACTCGTCCATC 19
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Db        574 CAGGGCAAACTCGTCCATC 556



X66858
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
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ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
            transposase.
SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
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  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
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COMMENT     On Jul 10, 2002 this sequence version replaced gi:262329.
FEATURES             Location/Qualifiers
     source          1. .1306
                     /organism="Bordetella parapertussis"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:519"
                     /clone="pRPP1"
     repeat_region   1. .1306
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                     EFALHKGHRYATVVVDPIGRQVLWIGPGRSRETARAFFEQLPPGAAQRIKAVAIDMTT
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                     LLRNRDNLDRQQAVRLDELLQANQPLLTVYVLRDELKRLWFYQRPAWARQAWNHWYEQ
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ORIGIN

  Query Match             100.0%;  Score 19;  DB 14;  Length 1306;
  Best Local Similarity   100.0%;  Pred. No. 1.3e+03;
  Matches   19;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GGTTGGCATACCGTCAAGA 19
              |||||||||||||||||||
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X66858
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
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Qy          1 GCTGGACAAGGCTCG 15
              |||||||||||||||
Db        490 GCTGGACAAGGCTCG 504
```

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"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. parapertussis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high

quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

20. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993 ; cited in the IDS) and Wittwer et al. (U.S. Patent No. 6,174,670), as applied to claim 40 above, and further in view Tyagi et al. (U.S. patent No. 5,925,517).

A) Regarding claim 45, Wittwer et al. teach the acceptor moiety, rhodamine, being a quencher (col. 30, lines 33, 34). Wittwer et al. do not teach probes forming a secondary structure which brings the donor and acceptor into spatial proximity.

B) Regarding claim 44, Tyagi et al. teach probes which contain a part complementary to a target and two parts on either side of the complement which can form a secondary structure when not hybridized to the target. The probes contain labels on either end of the probe. When the probe is not bound to the target, the labels are in close proximity, whereas in the presence of a target they become separated, changing the signal from the labels, which are FRET labels (Fig. 3; col. 4, lines 59-67; col. 5, lines 1-67; col. 6, lines 1-7; col. 16, lines 13-22, 41-59).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the probes of Tyagi et al. in the detection method of Van der Zee et al. and Wittwer et al. The motivation to do so, provided by Tyagi et al., would have been that unimolecular probes generated signal upon hybridization to nucleic acids, but no signal in the absence of hybridization (col. 3, lines 55-58), were used in real-time detection (col. 4, lines 5-8), did not

require expensive equipment (col. 4, lines 9-11) and distinguished between closely related nucleic acids (col. 4, lines 12-16).

21. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No references were found teaching or suggesting a probe with SEQ ID NO: 11, which differs by an insertion of a T into a sequence between bp 843-870 of the accession No. M22031:

gb|M22031.1|BPETERRA B.pertussis insertion sequence with 28 bp terminal inverted repeats
DNA
Length=1053

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 Score = 42.1 bits (21),  Expect = 0.054
 Identities = 28/29 (96%), Gaps = 1/29 (3%)
 Strand=Plus/Plus

Query  1    GACCAATGGCAAGGCTCGAACGCTTCATC  29
            ||||||||||||||| ||||||||||||
Sbjct  843  GACCAATGGCAAGGC-CGAACGCTTCATC  870
```

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
January 12, 2009